

The Importance of Research in Addressing the COVID-19 Pandemic:

Focus on the Use of Serology Testing

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Abstract

The Coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has resulted in a global health emergency with major social and economic disruption. With no effective treatment or vaccine available, and given the ease of transmission, it becomes critical to develop rapid diagnostic and tracer methodologies, while working to understand how the virus causes critically severe disease in about 5% of those affected. Clinical and translational research of patients impacted by COVID-19 is essential, and in this commentary, the focus is on the use of serology testing as a proxy for infection to better understand risk for health complications, and tailor treatment and vaccine immunization to high-risk groups. The rationale for studying pediatric patients is that there is a paucity of research in this vulnerable population and children have fewer co-morbidities, but similar health disparities and disease complications as compared to adults. Asymptomatic children could also transmit the virus to others within their households and communities; thus, knowledge of their rate of infection is important to help mitigate spread and a possible second wave of infection.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel SARS-CoV-2, was declared a pandemic on March, 12, 2020, and to date has infected over eight million people worldwide with over two million confirmed cases in the United States. Compared to adults, the percentage of children with COVID-19 is lower,¹ as are the level of severity and mortality rate.²⁻⁴ However, in both children and adults, COVID-19 disproportionately affects minority communities of low socioeconomic status, and certain co-morbidities increase the severity of disease in the elderly.

Background

Various studies in children have shown viral infection rates of 1-5%, with fever being the most commonly presenting symptom.³ It is not known if children are more resistant to infection or mount a more rapid or different immune response. In addition, are pediatric patients with chronic disease more susceptible to infection and increased severity of disease? Finally, do both asymptomatic and symptomatic children transmit the disease to others? The answers to these questions and others are emerging through numerous clinical and translational research studies conducted across the globe, and which depend on both viral and serology testing for accurate diagnosis to better understand the complexity of COVID-19.

Antibody response (IgG and IgM levels) against SARS-CoV-2 usually appears for most adult and pediatric patients at ten days or later after symptom onset, and Long et al.⁵ have shown 100% seroconversion 19 days after symptom onset. Serology testing is especially important in the design of vaccine studies and use of convalescent plasma or therapeutic monoclonal antibodies, and antibody status will be pivotal in guiding epidemiological measures to determine

at risk populations. Serology testing is also key to answering many questions regarding how infected individuals and populations respond to the virus, as well as serving as a proxy for viral infection. Several examples of the role serology testing has played in identifying and understanding the spectrum of new clinical morbidities associated with COVID-19 in pediatric patients are described below.

Serology Testing

DeBiasi et al.⁶ have shown that the youngest (<1 year) and oldest (adolescents/young adults) infected with SARS-CoV-2 were more likely to be hospitalized, and the oldest required critical intensive care. Their work also suggests that African American and Hispanic populations are more severely affected by COVID-19 and that children have multi-symptom involvement. Henry et al.⁷ confirmed elevated levels of C-reactive protein, procalcitonin, and lactate dehydrogenase in both mild and severely affected children. Elevation of creatine kinase MB in mild pediatric cases also indicates that there is cardiac involvement in this disease.

An unusual presentation of overlapping symptoms of Kawasaki disease and toxic shock syndrome occurred in previously healthy children first in Italy,⁸ followed by England⁹ and the U.S.¹⁰ in April 2020. Studies of children in France demonstrate that this disease, named multisystem inflammatory syndrome (MIS-C) associated with COVID-19, occurs at higher frequency in children of African descent and that symptoms also include gastrointestinal disorders, hemodynamic instability, myocarditis, and acute heart failure.¹¹⁻¹³ This multisystem condition presented itself several weeks after the peak of COVID-19 infection in each country. Interestingly, although many of these children tested negative for the virus, they were seropositive, indicating prior infection by SARS-CoV-2.

Dermatological conditions also seem to be a later stage reaction to SARS-CoV-2 infection. A delayed cutaneous manifestation of COVID-19 was described recently in a 7-year old child.¹³ These chilblains-like lesions were documented by telehealth visits to a general pediatric outpatient clinic and confirmed by pediatric dermatology. The patient tested negative for the virus, but positive for SARS-CoV-2 IgG antibodies, indicating prior infection.

What the above studies in the pediatric population have shown is to expect the unexpected with COVID-19. Without serology testing, the association between COVID-19 and MIS-C, as well as the unusual dermatological manifestations of this disease, may have been missed. Serology testing allows the ascertainment of prior infection and often is a quicker, more reliable proxy of infection than viral testing. As the transmission of the virus decreases and individuals recover, it becomes important to know who has been infected and to know short- and long-term clinical outcomes. Research is critical to prepare for a possible second wave of infection or for a different viral pandemic.

One of the unifying themes of these research studies is that a preexisting proinflammatory state seems to contribute to COVID-19 disease severity in both pediatric and adult populations. This raises the interesting question as to whether children, who have not developed many of the comorbidities of the adult population, can serve as models to understand disease susceptibility and morbidity associated with SARS-CoV-2, paving the way to better understanding of disease etiology and more effective therapies. Clinical and translational research into COVID-19 promises to provide some of these answers in addition to generating other clinical questions to drive further research efforts into understanding this complex disease.

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